FORM PTO-1390(Rev. 5-93) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 9052-67

U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5): 09/700057

| INTERNATIONAL APPLICATION NO. | INTERNATIONAL FILING DATE | PRIORITY DATE CLAIMED |
|---|---|---|
| PCT/GB99/01306 | May 13, 1999 | May 13, 1998 |

TITLE OF INVENTION

*DEXTRIN-CONTAINING COMPOSITION FOR PREVENTING SURGICAL ADHESIONS*

APPLICANT(S) FOR DO/EO/US

Colin BROWN

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. [X] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [X] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).

6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [X] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.

8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).

9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

**Items 11. to 16. below concern other document(s) or information included:**

11. [X] An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98.

12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.

14. [ ] A substitute specification.

15. [ ] A change of power of attorney and/or address letter.

16. [X] Other items or information: International Preliminary Examination Report; International Search Report; PCT Request

| U.S. APPLICATION NO (if known, see 37 CFR 1.5) | INTERNATIONAL APPLICATION NO | ATTORNEY'S DOCKET NUMBER |
|---|---|---|
| 09/700057 | PCT/GB99/01306 | 9052-67 |

| 17. [X] The following fees are submitted: | CALCULATIONS | PTO USE ONLY |
|---|---|---|
| **Basic National Fee (37 CFR 1.492(a)(1)-(5)):** Search Report has been prepared by the EPO or JPO . . . . . **$860.00** | | |
| International preliminary examination fee paid to USPTO (37 CFR 1.482). . . . . **$690.00** | | |
| No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) . . . . . **$710.00** | | |
| Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO. . . . . **$1,000.00** | | |
| International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4). . . . . **$100.00** | | |
| ENTER APPROPRIATE BASIC FEE AMOUNT = | $ **860.00** | |
| Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)). | $ | |

| Claims | Number Filed | Number Extra | Rate | | |
|---|---|---|---|---|---|
| Total Claims | 39-20 = | 19 | X **$18.00** | $ **342.00** | |
| Independent Claims | 3-3 = | 0 | X **$80.00** | $ | |
| Multiple dependent claim(s) (if applicable) | | | + **$270.00** | $ | |
| TOTAL OF ABOVE CALCULATIONS = | | | | **$1,202.00** | |
| Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28). | | | | $ | |
| SUBTOTAL = | | | | **$1,202.00** | |
| Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). | | | | $ | |
| TOTAL NATIONAL FEE = | | | | **$1,202.00** | |
| Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property + | | | | $ | |
| TOTAL FEES ENCLOSED = | | | | **$1,202.00** | |
| | | | | Amount to be refunded | $ |
| | | | | charged | $ |

a. [X] A check in the amount of **$1,202.00** to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 50-0220.

NOTE: **Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.**

SEND ALL CORRESPONDENCE TO:

Robert J. Smith, Esq.
Myers Bigel Sibley & Sajovec
Post Office Box 37428
Raleigh, North Carolina 27627

"Express Mail" mailing label number EL682671341US
Date of Deposit November 10, 2000

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Box PCT, Commissioner for Patents, Washington, DC 20231

Marjorie J. Pfeiffer
Marjorie J. Pfeiffer
Date of Signature November 10, 2000

SIGNATURE

Robert J. Smith

40,820
REGISTRATION NUMBER

Attorney's Docket No. 9052-67 PATENT

IN THE UNITED STATES DESIGNATED OFFICE (DO/US)

In re: Application of Colin Brown
Serial No.: To be Assigned
Filed: Concurrently Herewith
For: *DEXTRIN-CONTAINING COMPOSITION FOR PREVENTING SURGICAL ADHESIONS*

Date: November 10, 2000

BOX PCT
Commissioner for Patents
Washington, DC 20231

**PRELIMINARY AMENDMENT**

Sir:

Prior to the examination of the above application, please amend the above-identified application as follows:

**In the Title:**

Please delete the title.

Please insert therefor the following new title.

-- *SURGICAL COMPOSITIONS AND METHODS OF USING THE SAME* --

**In the Claims:**

In Claim 4, please delete "any preceding claim" and insert therefor -- Claim 1 --.

In Claim 6, please delete "any preceding claim" and insert therefor -- Claim 1 --.

In Claim 8, please delete "any preceding claim" and insert therefor -- Claim 1 --.

In Claim 10, please delete "any of Claims 1-9" and insert therefor -- Claim 1 --.

In Claim 11, please delete "any preceding claim" and insert therefor -- Claim 1 --.

In Claim 12, please delete "any of Claims 1-10" and insert therefor -- Claim 1 --.

In Claim 14, please delete "any preceding claim" and insert therefor -- Claim 1 --.

In Claim 16, please delete "either of Claims 14 or 15" and insert therefor -- Claim 14 --.

In Claim 17, please delete "any preceding claim" and insert therefor -- Claim 1 --.

In Claim 19, please delete "any preceding claim" and insert therefor -- Claim 1 --.

In Claim 21, please delete "any preceding claim" and insert therefor -- Claim 1 --.

In Claim 22, please delete "any preceding claim" and insert therefor -- Claim 1 --.

In Claim 26, please delete "any of Claims 23-25" and insert therefor -- Claim 23 --.

In Claim 27, please delete "any of Claims 23-26" and insert therefor -- Claim 23 --.

In Claim 28, please delete "any of Claims 23-27" and insert therefor -- Claim 23 --.

In Claim 29, please delete "any of Claims 23-28" and insert therefor -- Claim 23 --.

In Claim 30, please delete "any of Claims 23-29" and insert therefor -- Claim 23 --.

In Claim 32, please delete "any of Claims 23-31" and insert therefor -- Claim 23 --.

In Claim 34, please delete "either of Claims 32 or 33" and insert therefor -- Claim 32 --.

In Claim 35, please delete "any of Claims 23-34" and insert therefor -- Claim 23 --.

39. (Amended) Products containing an aqueous formulation of the polysaccharide dextrin and **[any one or more of the features of Claims 17-22]** a feature recited by Claim 17 as a combined preparation for use in preventing or reducing the incidence of adhesions in or associated with a

body cavity wherein the dextrin contains more than 15% of polymers with a degree of polymerisation (DP) greater than 12 and acts as an osmotic agent to maintain a volume of the aqueous formulation in the body cavity serving to separate tissues which otherwise may adhere to each other.

**REMARKS**

Claims 1-39 are presented for examination. The above claims have been amended to better conform to U.S. practice. Applicants respectfully request that this amendment be entered prior to calculation of the claim fees.

Applicants note that these claims were deemed to fulfill novelty and inventive step requirements as set forth in the PCT International Preliminary Examination Report. Accordingly, it is believed that these claims are in condition for allowance, action of which is respectfully requested.

Respectfully submitted,

Robert J. Smith
Registration No. 40,820

Correspondence Address:
USPTO Customer No.: **20792**
Myers Bigel Sibley & Sajovec
Post Office Box 37428
Raleigh, NC 27627
Telephone (919) 854-1400
Facsimile (919) 854-1401

"Express Mail" mailing label number EL682671341US
Date of Deposit: November 10, 2000

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Box PCT, Commissioner for Patents, Washington, DC 20231.

Marjorie J. Pfeiffer
Date of Signature: November 10, 2000

# DEXTRIN-CONTAINING COMPOSITION FOR PREVENTING SURGICAL ADHESIONS

This invention relates to the prevention of surgical adhesions, and in particular to adhesions taking place in serous cavities including the peritoneum, the pericardium, the plura and synovial cavities such as joints and tendons and to adhesions following spinal and/or cranial operations. Reference will be made hereinbelow to the prevention of adhesions in the peritoneum but it should be understood that the present invention has applicability in connection with other serous cavities in both humans and animals.

Abdominal surgery is a rapidly changing field. Many forms of open surgery are being increasingly replaced by laparoscopic procedures. Although considerable immediate post-surgical benefits have been demonstrated to follow from laparoscopic surgery, the incidence of adhesions has not decreased. The severe drying of the mesothelium which results from prolonged exposure of the peritoneum to dry gases (pneumoperitoneum of 2-4 hours), may give rise to a higher incidence of global peritoneal adhesions than has hitherto been encountered in open surgery. Many gynaecologists with long experience of laparoscopic surgery consider that both open and closed surgery have equally high incidences of adhesions.

WO 92/21354 describes a surgical adhesion as the attachment of organs or tissues to each other through scar tissue. A formation of scar tissue is described as a normal sequel to surgery or other tissue injury and is required for proper wound healing. In some cases, however, the scar tissue overgrows the intended region and creates surgical adhesions. These scar tissue surgical adhesions restrict the normal mobility and function of affected body parts. The invention disclosed in WO 92/21354 is based on the discovery that anionic polymers effectively inhibit invasion of cells associated with detrimental healing processes, ie, fibrosis, and scaring. In particular, certain inhibitory anionic polymers are useful to inhibit fibroblast invasion, thus regulating the healing process and preventing fibrosis. Anionic polymers specified in WO 92/21354 include dextran sulfate, pentosan polysulfate as well as natural

proteoglycans, or the glycosaminoglycan moieties of proteoglycans, including dermatan sulfate, chondroitin sulfate, keratan sulfate, heparan sulfate, heparin and alginate.

By attempting to inhibit fibroblast invasion, the approach of WO 92/21354 is one of post-adhesion treatment since fibroblast invasion is a later stage, that is to say, it occurs after formation of the adhesion. The invention of WO 92/21354 attempts to prevent the adhesion becoming permanent. By contrast the present invention is concerned with the prevention of the occurrence of an adhesion.

According to a first aspect of the present invention there is provided a method of preventing or reducing the incidence of adhesions in or associated with a body cavity comprising an aqueous formulation containing the polysaccharide dextrin in an amount effective to prevent or reduce such adhesions, wherein the dextrin contains more than 15% of polymers with a degree of polymerisation (DP) greater than 12 and acts as an osmotic agent to maintain a volume of the aqueous formulation in the body cavity serving to separate tissues which otherwise may adhere to each other.

The term "dextrin" means a glucose polymer which is produced by the hydrolysis of starch and which consists of glucose units linked together by means mainly of α-1,4 linkages. Typically dextrins are produced by the hydrolysis of starch obtained from various natural products such as wheat, rice, maize and tapioca. In addition to α-1,4 linkages, there may be a proportion of α-1,6 linkages in a particular dextrin, the amount depending on the starch starting material. Since the rate of biodegradability of α-1,6 linkages is typically less than that for α-1,4 linkages, it is preferred that, for many applications, the percentage of α-1,6 linkages is less than 10% and more preferably less than 5%.

Any dextrin is a mixture of polyglucose molecules of different chain lengths. As a result no single number can adequately characterise the molecular weight of such a polymer. Accordingly, various averages are used, the most common being the weight average molecular weight (Mw) and the number average molecular weight (Mn). Mw is particularly sensitive to changes in the high molecular weight content

of a polymer whilst Mn is largely influenced by changes in the low molecular weight content of the polymer.

It is preferred that the Mn of the dextrin is in the range of from 1,000 to 30,000 and ideally the Mw is in the range of from 3,000 to 50,000. More preferably, the Mn is from 3,000 to 8,000 and the Mw is from 5,000 to 50,000.

The term "degree of polymerisation" (DP) can also be used in connection with polymer mixtures. For a single polymer molecule, DP means the number of polymer units. For a mixture of molecules of different DP's, weight average DP and number average DP correspond to Mw and Mn. In addition, DP can also be used to characterise a polymer by referring to the polymer mixture having a certain percentage of polymers of DP greater than a particular number or less than a particular number.

It is preferred that the dextrin contains more than 15% of polymers of DP greater than 12 and, more preferably, more than 50% of polymers of DP greater than 12.

The dextrin used in the present invention is water soluble or at least forms a solution in water or a gel formulation. The dextrin used in this invention may be in the form of either unsubstituted dextrin (as obtained by the hydrolysis of starch) or may be substituted by one or more different groups. The substituents may be negatively charged groups, for instance, sulfate groups, neutral groups, or positively charged groups, for instance, quaternary ammonium groups. In the case where the substituent group is sulfate, it is preferred that the sulfated polysaccharide contains at least one sulfate group per saccharide (glucose) unit.

The present invention also provides a composition for preventing or reducing the incidence of adhesions in or associated with a body cavity comprising an aqueous formulation containing the polysaccharide dextrin in an amount effective to prevent or reduce such adhesions, wherein the dextrin contains more than 15% of polymers

with a degree of polymerisation (DP) greater than 12 and acts as an osmotic agent to maintain a volume of the aqueous formulation in the body cavity serving to separate tissues which otherwise may adhere to each other.

The present invention further provides the use of a composition for preventing or reducing the incidence of adhesions in or associated with a body cavity comprising an aqueous formulation containing the polysaccharide dextrin in an amount effective to prevent or reduce such adhesions, wherein the dextrin contains more than 15% of polymers with a degree of polymerisation (DP) greater than 12 and acts as an osmotic agent to maintain a volume of the aqueous formulation in the body cavity serving to separate tissues which otherwise may adhere to each other.

The present invention further provides the use of the polysaccharide dextrin in the manufacture of a composition comprising an aqueous solution or gel formulation of dextrin for preventing or reducing adhesions in humans and animals.

Dextrin is a useful material for the production of an adhesion-preventing composition because, *inter alia*, it is non-toxic, cheap and has the ability to hold fluid in a body cavity. It is also readily metabolised within the body.

Preferably, a composition of the invention is applied to the appropriate body cavity or area after the operation has been carried out.

Preferably, the composition of the present invention is allowed to remain in the body cavity for a minimum of 2 to 3 days and especially over the period during which fibrin exudation is at a maximum. More preferably, the composition should remain in the body cavity for a period of up to 7 to 8 days in order to allow restoration of non-stick surfaces (mesothelium regeneration).

Preferably, a composition of the invention should be applied to the body cavity in a volume large enough to keep the surfaces apart. For the peritoneum, the volume should preferably be in the range 500-2000 ml and, more preferably, about 1000 ml-1500 ml.

Preferably, the composition should be applied to the appropriate body cavity or area in differing concentrations ideally over a concentration range of 2.5-18% and more ideally over a concentration range of 3-5% and most ideally at about 4% by weight, said concentration range is selected for a specified time span, even more ideally the concentration range is selectively altered over a period of time.

Preferably, the composition should include a concentration of dextrin which is such that the fluid largely holds in place over the period it resides in the cavity. Where a composition includes 4% by weight of dextrin then a suitable dwell period for one infusion might be of the order of 2 to 3 days. A high concentration is liable to cause ingress of fluid. A second infusion at day 3 may extend the total dwell period from 6 to 7 days.

Alternatively, a composition having a dextrin concentration of from 12 to 15% by weight may be used in a smaller volume (perhaps about 750 ml) and will be subject to ingress of fluid. However a single infusion might be sufficient for the full 6 to 7 day period.

Comparing dextrin with dextran, the latter has relatively poor biocompatibility. It is subject to immunological hypersensitivity due to its concentration in lymph nodes and its lack of metabolisability. At best, a dextran solution or suspension will act not so much to separate surfaces and therefore prevent adhesions but simply as a lubricant. Dextrin advantageously serves as an osmotic agent, which can maintain the volume of a solution in the peritoneal cavity. The continued presence of the dextrin solution within the cavity serves to separate tissues which otherwise may adhere to each other.

The use of a solution or gel formulation of dextrin is also advantageous by comparison with a prior art technique which makes use of synthetic films in the form of patches which are applied to particular areas where maximum damage has occurred. However, in the case of a body cavity, such as the peritoneum, the damage is liable to occur as well at a distance from the operative site, especially in

laparoscopy, due to the drying which takes place. In some instances global damage over an area of as much as two square metres can take place.

In responding to a wound, the body causes circulating fibrinogen to form fibrin and it is this production of fibrin which is associated with the formation of adhesions. Calcium ions are required to polymerise fibrinogen to fibrin and, accordingly, a composition of the present invention may include a calcium binding agent such as EDTA or sodium citrate.

A composition of the present invention may include a suitable lubricant such as a phosphospholipid.

A composition of the present invention may include a hyaluronate or glycocosolaminoglycan or a material which is associated with serosal lubrication and which has strong anti-adhesive properties. In this case the dextrin solution or gel formulation is effective in spreading the hyaluronate throughout the whole peritoneum.

A composition of the present invention may include an antibiotic agent or a material/agent which is associated with preventing an infection or build up of bacteria or foreign bodies or the like. A composition including such a material/agent would be particularly advantageous in prevention or amelioration of pelvic inflammatory disease.

A composition of the present invention may also include a fibrinolytic agent or an analogue thereof, an anti-inflammatory agent or an analogue thereof, dextrin sulphate and/or methylene blue.

The present invention provides a preferred composition comprising an aqueous solution or gel formulation of dextrin, one or more phosphospholipids and

hyaluronate. Such a composition is not only highly effective in preventing adhesions but also has a good shelf life.

Mesothelial secretion of prostacyclin has been demonstrated and this activity enhances the non-stick properties of the mesothelium. The present invention provides a composition comprising dextrin together with prostacyclin or an analogue thereof.

According to a further aspect of the invention there is provided a biocompatible, bioresorbable. and non-toxic adhesion prevention kit for surgical use in humans or animals, comprising an aqueous solution or gel formulation of dextrin as hereinbefore described, and optionally or additionally comprising a calcium binding agent as hereinbefore described and/or a suitable lubricant as hereinbefore described and/or prostacyclin or an analogue thereof as hereinbefore described and/or an antibiotic agent as hereinbefore described..

## EVIDENCE IN SUPPORT OF THE INVENTION

PROTOCOL:

Animals: One hundred thirty, female New Zealand White rabbits, 2.4-2.7 kg, were purchased from Irish Farms (Norco, CA) and quarantined in the USC Vivaria for at least 2 days prior to use. Ten rabbits were randomised into thirteen treatment groups prior to initiation of surgery. The rabbits were housed on a 12:12 light:dark cycle with food and water available *ad libitum*.

Materials: The solutions (7.5% [wt/vol] icodextrin-Lot # 98A06G33, 20% [wt/vol] icodextrin-Batch # SP184772 and placebo (electrolyte solution for icodextrin)-Batch # SP184829 were supplied by ML Laboratories Plc. Icodextrin is a [1 → 4] - α - Glucan having more than 85% of its molecules with molecular weights between 1,640 - 45,000 with a weight average molecular weight of approximately 20,000. The placebo electrolyte solution contained 5.4g sodium chloride, 4.5g sodium lactate, 257 mg calcium chloride, 51 mg magnesium chloride in 1 litre water for injection. The sutures used to close the muscle and skin were 3-0 coated Dexon II suture (Davis and Geck, Manati, PR).

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Double Uterine Horn Model: Rabbits were anaesthetised with a mixture of 55 mg/kg ketamine hydrochloride and 5 mg/kg Rompum intramuscularly. Following preparation for sterile surgery, a midline laparotomy was performed. The uterine horns were exteriorised and traumatised by abrasion of the serosal surface with gauze until punctuate bleeding developed. Ischaemia of both uterine horns was induced by removal of the collateral blood supply. The remaining blood supply to the uterine horns was the ascending branches of the utero-vaginal arterial supply of the myometrium. At the end of surgery, 10 to 75 ml (10, 25, 50, 75 ml) of 7.5% or 20% icodextrin, 10 or 75 ml placebo or no treatment (control) was administered. After 7 days, the rabbits were terminated and the percentage of the area of the horns adherent to the various organs was determined. In addition, the tenacity of the adhesions was scored using the following system:

0 = No adhesions;
1 = Mild, easily dissectable adhesions;
2 = Moderate adhesions; non-dissectable, does not tear the organ;
3 = Dense adhesions; non-dissectable, tears organ when removed.

In addition an overall score which takes into account all of the above data was given to each rabbit. The following scoring system was used:

0 No adhesions;
0.5+ Light, filmy pelvic adhesions involving only one organ, typically ony 1 or 2 small adhesions;
1.0+ Light, filmy adhesions, not extensive although slightly more extensive than 0.5;
1.5+ Adhesions slightly tougher and more extensive than a 1 rating;
2.0+ Tougher adhesions, a little more extensive, uterine horns usually have adhesions to both bowel and bladder;
2.5+ Same as 2, except the adhesions are usually not filmy at any site and more extensive;

3.0+ Tougher adhesions than 2, more extensive, both horns are attached to the bowel and bladder, some movement of the uterus possible;

3.5+ Same as 3, but adhesions slightly more extensive and tougher;

4.0+ Severe adhesions, both horns attached to the bowel and bladder, unable to move the uterus without tearing the adhesions.

The rabbits were scored by two independent observers that were blinded to the prior treatment of the animal. If there was disagreement as to the score to be assigned to an individual animal, the higher score was given.

Statistical Analysis: The tenacity and overall scores were analysed by rank order analysis and analysis of variance on the ranks. The percentage area of the horns involved to the various organs was compared by Student's t test. The data from the incidence of adhesion formation was analysed by Chi square analysis. The comparison with placebo shown on Table 14 was done between the 10 ml placebo group and data from animals which received 10-25 ml of icodextrin or between the 75 ml placebo group and data from animals which received 50 or 75 ml icodextrin.

RESULTS: One rabbit from the group treated with 50 ml 20% icodextrin died postoperatively without evidence of inflammation or oedema at necropsy and was replaced. During the postoperative evaluation of the rabbits, it was noted that several rabbits given the higher volumes of icodextrin had "bulging" abdomens for the first few postoperative days. This occurred in 3 rabbits which received 75 ml or 7.5% icodextrin and 8 rabbits which received 75 ml of 20% icodextrin. The bulging was observed for 24 hours in the rabbits which received 7.5% icodextrin and 48-72 hours in the rabbits which received 20% icodextrin. This bulging was not observed in the group of rabbits which received 75 ml of placebo. No excess fluid was observed in any icodextrin or placebo-treated rabbits at necropsy. One rabbit, which received 75 ml of 20% icodextrin, had a small amount of subcutaneous fluid at necropsy.

The effect of icodextrin on the formation of adhesions in this rabbit model can be found in Tables 1-13. The effect of icodextrin on the incidence of adhesions can be found in Table 14. For each site, the extent and tenacity (tenacity in parentheses) of the adhesions between the horn and that site were given. In the final row of each column (with the exception of the column on the far right), the mean and standard error of the mean for the extent score for each site is given. In the final row of the final column, the mean and standard error of the mean of the ranks is given. If an extent or rank order was reduced compared to control ($p \leq 0.05$), a * is in the appropriate row. At higher volumes (25 to 75 ml) of icodextrin, there was a significant reduction in the formation of adhesions. However, no difference between the 7.5% and 20% solutions was noted in this study. This efficacy is in the absence of inflammation noted with some materials implanted intraperitoneally.

In conclusion results demonstrated that high volumes of icodextrin (both percentages) were highly efficacious in the reduction of adhesion formation in this model with efficacy noted after administration of 50 ml or 75 ml of icodextrin. The lower volumes of icodextrin have less effect and the placebo had no effect on adhesion formation. Thus we have demonstrated that the composition of the present invention is effective in reducing the incidence of post-operative adhesion formation.

**Amended Claims**

1. A composition for preventing or reducing the incidence of adhesions in or associated with a body cavity comprising an aqueous formulation containing the polysaccharide dextrin in an amount effective to prevent or reduce such adhesions, wherein the dextrin contains more than 15% of polymers with a degree of polymerisation (DP) greater than 12 and acts as an osmotic agent to maintain a volume of the aqueous formulation in the body cavity serving to separate tissues which otherwise may adhere to each other.

2. A composition according to Claim 1 wherein the aqueous formulation is a solution.

3. A composition according to Claim 1 wherein the aqueous formulation is a gel.

4. A composition according to any preceding claim wherein the percentage of α-1,6 linkages in the dextrin is less than 10%.

5. A composition according to Claim 4 wherein the percentage of α-1,6 linkages in the dextrin is less than 5%.

6. A composition according to any preceding claim wherein the number average molecular weight (Mn) of the dextrin is in the range 1,000 to 30,000.

7. A composition according to Claim 6 wherein the Mn of the dextrin is in the range 3,000 to 8,000.

8. A composition according to any preceding claim wherein the weight average molecular weight (Mw) the of dextrin is in the range 3,000 to 50,000.



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9. A composition according to Claim 8 wherein the Mw of the dextrin is from 5,000 to 50,000.

10. A composition according to any of Claims 1-9 wherein the dextrin contains more than 50% of polymers with a degree of polymerisation (DP) greater than 12.

11. A composition according to any preceding claim wherein the dextrin is unsubstituted dextrin.

12. A composition according to any of Claims 1-10 wherein the dextrin is substituted by one or more different groups selected from the group consisting of negatively charged groups, sulfate groups, neutral groups, positively charged groups and quaternary ammonium groups.

13. A composition according to Claim 12 wherein the dextrin is sulfated dextrin containing at least one sulfate group per saccharide (glucose) unit.

14. A composition according to any preceding claim in which the dextrin is present in an amount of from 2.5-18 % by weight of the composition.

15. A composition according to Claim 14 in which the dextrin is present in an amount of from 3-5 % by weight of the composition.

16. A composition according to either of Claims 14 or 15 in which the dextrin is present in an amount of about 4 % by weight of the composition.

17. A composition according to any preceding claim which further includes a calcium binding agent.



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18. A composition according to Claim 17 wherein the calcium binding agent is either EDTA or sodium citrate.

19. A composition according to any preceding claim which further includes a suitable lubricant.

20. A composition according to Claim 19 wherein the lubricant is a phospholipid.

21. A composition according to any preceding claim which further includes a hyaluronate.

22. A composition according to any preceding claim which further includes a compound selected from one or more of the following compounds, glycosolaminoglycan, an antibiotic agent, prostacyclin or an analogue thereof, a fibrinolytic agent or an analogue thereof, an anti-inflammatory agent or an analogue thereof, dextrin sulphate and/or methylene blue.

23. A method of preventing or reducing the incidence of adhesions in or associated with a body cavity, which comprises introducing into the body cavity an aqueous formulation containing the polysaccharide dextrin in an amount effective to prevent or reduce the incidence of such adhesions, wherein the dextrin contains more than 15% of polymers with a degree of polymerisation (DP) greater than 12 and acts as an osmotic agent to maintain a volume of the aqueous formulation in the body cavity serving to separate tissues which otherwise may adhere to each other.

24. A method according to Claim 23 wherein the aqueous formulation is a solution.

25. A method according to Claim 23 wherein the aqueous formulation is a gel.



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26. A method according to any of Claims 23-25 wherein said composition is applied to the appropriate body cavity after a surgical operation has been carried out.

27. A method according to any of Claims 23-26 wherein the composition is allowed to remain in the body cavity for a minimum of 2 to 3 days.

28. A method according to any of Claims 23-27 wherein the composition is allowed to remain in the body cavity over the period during which fibrin exudation is at a maximum.

29. A method according to any of Claims 23-28 wherein the composition remains in the body cavity for a period of up to 7 to 8 days in order to allow restoration of non-stick surfaces (mesothelium regeneration).

30. A method according to any of Claims 23-29 wherein the composition is applied to the peritoneal cavity in a volume in the range 500-2000 ml.

31. A method according to Claim 30 wherein the composition is applied to the peritoneal cavity in a volume in the range 1000 ml-1500 ml.

32. A method according to any of Claims 23-31 wherein the dextrin is applied to the appropriate body cavity in differing concentrations over a concentration range of 2.5-18 % by weight of the composition.

33. A method according to Claim 32 wherein the dextrin is applied to the appropriate body cavity in differing concentrations over a concentration range of 3-5 % by weight of the composition.

34. A method according to either Claims 32 or 33 wherein the dextrin is applied to the appropriate body cavity in an amount of about 4 % by weight of the composition.

35. A method according to any of Claims 23-34 wherein the concentration range of the dextrin is selectively altered over a period of time.

36. A biocompatible, bioresorbable, and non-toxic adhesion prevention kit for surgical use in humans or animals, comprising an aqueous formulation of dextrin.

37. A kit according to Claim 36 wherein the aqueous formulation is either a solution or a gel.

38. Use of a composition according to Claim 1 and optionally including any one or more of the features of Claims 2-22 for preventing or reducing the incidence of adhesions in or associated with a body cavity which comprises introducing into the body cavity an aqueous formulation containing the polysaccharide dextrin wherein the dextrin contains more than 15% of polymers with a degree of polymerisation (DP) greater than 12 and acts as an osmotic agent to maintain a volume of the aqueous formulation in the body cavity serving to separate tissues which otherwise may adhere to each other.

39. Products containing an aqueous formulation of the polysaccharide dextrin and any one or more of the features of Claims 17-22 as a combined preparation for use in preventing or reducing the incidence of adhesions in or associated with a body cavity wherein the dextrin contains more than 15% of polymers with a degree of polymerisation (DP) greater than 12 and acts as an osmotic agent to maintain a volume of the aqueous formulation in the body cavity serving to separate tissues which otherwise may adhere to each other.

Table 1. Data from Surgical control Rabbits
% Horn Involved

| Right Horn | | | | Left Horn | | | | |
|---|---|---|---|---|---|---|---|---|
| Bowel | Bladder | Itself | Left | Bowel | Bladder | Itself | Right | Overall |
| 30(2) | 30(2) | 30(1) | 40(1) | 30(2) | 30(2) | 30(1) | 40(1) | 2.5+ |
| 30(1) | 30(1) | 50(2) | 50(2) | 30(1) | 30(1) | 30(1) | 50(2) | 2.5+ |
| 30(2) | 30(1) | 40(2) | 40(2) | 30(2) | 30(2) | 40(2) | 40(2) | 3.0+ |
| 40(1) | 20(1) | 50(2) | 30(1) | 40(1) | 20(1) | 30(1) | 30(1) | 3.0+ |
| 20(1) | 30(1) | 50(2) | 40(2) | 20(1) | 30(1) | 50(2) | 40(2) | 3.0+ |
| 40(1) | 30(1) | 50(1) | 40(1) | 40(1) | 30(1) | 60(1) | 40(1) | 3.5+ |
| 40(1) | - | 50(1) | 40(2) | 40(1) | - | 50(1) | 40(1) | 3.0+ |
| 40(1) | 20(1) | 50(1) | 40(1) | 40(1) | 20(1) | 40(2) | 40(1) | 3.0+ |
| 40(2) | 20(2) | 40(2) | 30(2) | 40(2) | 20(2) | 50(1) | 30(2) | 3.5+ |
| 40(1) | 20(1) | 60(1) | 50(1) | 40(1) | 20(1) | 60(1) | 50(1) | 3.0+ |
| 31±3.7 | 23±3.0 | 47±2.6 | 40±2.1 | 34±3.7 | 23±3.0 | 44±3.7 | 40±2.1 | 111.2±4.0 |

Table 2. Data from 10ml Placebo Rabbits
% Horn Involved

| Right Horn | | | | Left Horn | | | | |
|---|---|---|---|---|---|---|---|---|
| Bowel | Bladder | Itself | Left | Bowel | Bladder | Itself | Right | Overall |
| 30(1) | 20(1) | 50(2) | 30(1) | 30(1) | 20(1) | 40(2) | 30(1) | 2.5+ |
| 50(2) | 50(2) | 60(1) | 30(2) | 50(2) | 50(2) | 60(1) | 30(2) | 3.5+ |
| 40(2) | - | 50(1) | 20(2) | 40(2) | - | 50(1) | 20(2) | 3.0+ |
| 20(1) | - | 30(1) | 20(1) | 20(1) | - | 30(1) | 20(2) | 1.5+ |
| - | 30(2) | 40(1) | 40(2) | - | 30(2) | 40(1) | 40(2) | 2.5+ |
| 50(1) | 20(1) | 40(2) | 30(1) | 50(1) | 20(1) | 50(1) | 30(1) | 3.0+ |
| 30(2) | - | 20(2) | 40(2) | 30(2) | - | 20(2) | 40(2) | 3.0+ |
| 30(2) | - | 30(2) | 40(1) | 30(2) | - | 50(2) | 40(1) | 3.0+ |
| 50(2) | - | 40(1) | 50(2) | 50(2) | - | 40(1) | 50(2) | 3.0+ |
| 30(2) | 20(2) | 30(1) | 40(1) | 30(2) | 20(2) | 50(1) | 40(1) | 2.5+ |
| 33±5.0 | 14±5.4 | 39±3.9 | 34±3.0 | 33±5.0 | 14±5.4 | 43±3.7 | 34±3.1 | 100.7±7.5 |

Table 3. Data from 75ml Placebo Rabbits
% Horn Involved

| Right Horn | | | | Left Horn | | | | |
|---|---|---|---|---|---|---|---|---|
| Bowel | Bladder | Itself | Left | Bowel | Bladder | Itself | Right | Overall |
| 40(2) | 30(2) | 50(2) | 40(2) | 40(20) | 30(2) | 40(3) | 40(2) | 3.5+ |
| - | - | 50(1) | 20(1) | - | - | 40(1) | 20(1) | 2.5+ |
| - | 40(2) | 30(10) | 40(2) | - | 40(2) | 40(2) | 40(2) | 3.0+ |
| 40(1) | 20(1) | 50(1) | 20(1) | 40(1) | 20(1) | 50(1) | 20(1) | 3.0+ |
| 20(1) | - | 40(1) | 20(1) | 20(1) | - | 30(1) | 20(1) | 2.0+ |
| - | 10(1) | 20(1) | 40(1) | - | 10(1) | 40(1) | 40(1) | 2.0+ |
| - | 30.2 | 50(2) | 40(2) | - | 30(2) | 50(2) | 40(2) | 3.0+ |
| 40(1) | 20(1) | 50(1) | 20(1) | 40(1) | 20(1) | 30(1) | 20(1) | 2.5+ |
| 20(1) | - | 60(1) | 50(1) | 20(1) | - | 50(1) | 50(1) | 3.0+ |
| 20(2) | 10(1) | 40(1) | 30(1) | 20(2) | 10(1) | 50(2) | 30(1) | 3.0+ |
| 18±5.5 | 16±4.5 | 44±3.7 | 32±3.6 | 18±5.5 | 16±4.5 | 42±7.9 | 32±3.6 | 100.5±6.8 |

Table 4. Data from 10ml 7.5% Icodextrin Rabbits
% Horn Involved

| Right Horn | | | | Left Horn | | | | |
|---|---|---|---|---|---|---|---|---|
| Bowel | Bladder | Itself | Left | Bowel | Bladder | Itself | Right | Overall |
| 30(1) | 20(1) | 50(1) | 40(1) | 30(1) | 20(1) | 50(1) | 40(1) | 2.5+ |
| 40(1) | 30(1) | 50(1) | 40(2) | 40(1) | 30(1) | 50(1) | 40(2) | 3.0+ |
| 40(1) | 10(1) | 30(1) | 10(1) | 40(1) | 10(1) | 10(1) | 10(1) | 2.0+ |
| 30(1) | 20(1) | 30(2) | 30(1) | 30(1) | 20(1) | 30(2) | 30(1) | 2.5+ |
| - | - | 10(1) | 10(1) | - | - | 10(1) | 10(1) | 1.0+ |
| 40(2) | 20(1) | 50(1) | 30(1) | 40(2) | 20(1) | 50(2) | 30(1) | 3.5+ |
| - | 10(1) | 40(1) | 40(2) | - | 10(1) | 50(1) | 40(2) | 2.5+ |
| - | 30(2) | 30(1) | 40(2) | - | 30(2) | 50(2) | 40(2) | 3.0+ |
| 30(2) | - | 50(1) | 30(1) | 30(2) | - | 40(1) | 30(1) | 2.5+ |
| 30(2) | - | 10(1) | 30(1) | 30(2) | - | 50(1) | 30(1) | 2.5+ |
| 24±5.4 | 14±3.7 | 35±5.0 | 30±3.7 | 24±5.4 | 14±3.7 | 39±5.3 | 30±3.7 | 88.8±9.3 * |

Table 5. Data from 15ml 7.5% Icodextrin Rabbits
% Horn Involved

| Right Horn | | | | Left Horn | | | | |
|---|---|---|---|---|---|---|---|---|
| Bowel | Bladder | Itself | Left | Bowel | Bladder | Itself | Right | Overall |
| 20(1) | 10(1) | 40(1) | 40(1) | 20(1) | 10(1) | 40(1) | 40(1) | 2.5+ |
| 10(1) | - | 30(1) | 30(1) | 10(1) | - | 30(1) | 30(1) | 2.0+ |
| 30(2) | 30(2) | 40(1) | 20(1) | 30(2) | 30(2) | 40(1) | 20(2) | 2.5+ |
| 10(1) | 20(1) | 30(1) | 10(1) | 10(1) | 20(1) | 30(1) | 10(1) | 2.0+ |
| 30(1) | 30(1) | 40(1) | 30(1) | 30(1) | 30(1) | 40(1) | 30(1) | 2.5+ |
| 40(1) | 10(1) | 50(1) | 50(1) | 40(1) | 10(1) | 50(1) | 50(1) | 3.0+ |
| - | 20(1) | 30(1) | 20(1) | - | 20(1) | 30(1) | 20(1) | 1.5+ |
| 20(1) | 10(1) | 30(1) | 10(1) | 20(1) | 10(1) | 30(1) | 10(1) | 1.5+ |
| 30(2) | 30(2) | 40(1) | 10(1) | 30(2) | 30(2) | 50(1) | 10(1) | 2.5+ |
| - | 30(1) | 40(1) | 30(2) | - | 30(1) | 50(2) | 30(2) | 2.5+ |
| 19±4.3 * | 19±3.5 | 37±2.1 * | 25±4.3 * | 19±4.3 * | 19±3.5 | 39±2.8 | 25±4.3 * | 78.2±7.0 * |

Table 6. Data from 25ml 7.5% Icodextrin Rabbits
% Horn Involved

| Right Horn | | | | Left Horn | | | | |
|---|---|---|---|---|---|---|---|---|
| Bowel | Bladder | Itself | Left | Bowel | Bladder | Itself | Right | Overall |
| 10(1) | - | 30(1) | 20(1) | 10(1) | - | 30(1) | 20(1) | 1.5+ |
| - | - | 40(1) | - | - | - | 40(1) | - | 1.0+ |
| 10(1) | - | 30(1) | 20(2) | 10(1) | - | 30(1) | 20(1) | 2.0+ |
| 10(1) | - | 30(1) | 10(1) | 10(1) | - | 30(1) | 10(1) | 2.0+ |
| - | - | 10(1) | 10(1) | - | - | - | 10(1) | 1.0+ |
| - | - | 30(1) | - | - | - | 10(1) | - | 1.0+ |
| - | - | 20(1) | 40(1) | - | - | 30(2) | 40(1) | 2.0+ |
| 40(1) | 30(1) | 30(1) | 10(1) | 40(1) | 30(1) | 30(1) | 10(1) | 2.5+ |
| 10(1) | - | 20(1) | 10(1) | 10(1) | - | 30(1) | 10(1) | 1.5+ |
| 30(1) | | 30(1) | 30(1) | 30(1) | - | 40(1) | 30(1) | 2.0+ |
| 11±4.3 * | 3±3.0 * | 27±2.6 * | 15±4.0 * | 11±4.3 * | 3±3.0 * | 27±3.0 * | 15±4.0 * | 50.6±7.6 * |

Table 7. Data from 50ml 7.5% Icodextrin Rabbits
% Horn Involved

| Right Horn | | | | Left Horn | | | | |
|---|---|---|---|---|---|---|---|---|
| Bowel | Bladder | Itself | Left | Bowel | Bladder | Itself | Right | Overall |
| - | - | 30(1) | 10(1) | - | - | 30(1) | 10(1) | 1.0+ |
| - | - | 20(1) | 10(1) | - | - | 20(1) | 10(1) | 1.0+ |
| 10(1) | - | 30(1) | - | 10(1) | - | 30(1) | - | 1.0+ |
| - | - | 20(1) | 10(1) | - | - | 20(1) | 10(1) | 1.0+ |
| - | - | 30(2) | 10(1) | - | - | 30(2) | 10(1) | 1.5+ |
| 20(1) | 10(1) | 10(1) | - | 20(1) | - | - | - | 1.0+ |
| - | 10(1) | 30(2) | 40(2) | - | 10(1) | 30(2) | 40(2) | 2.5+ |
| 30(1) | - | 40(1) | 10(1) | 30(1) | - | 10(1) | 10(1) | 2.0+ |
| 10(1) | 10(2) | 10(1) | 10(1) | 10(1) | 10(2) | 10(1) | 10(1) | 1.5+ |
| - | - | 20(1) | 30(1) | - | - | 40(1) | 30(1) | 1.5+ |
| 7±3.4 * | 3±1.5 * | 24±3.1 * | 13±4.0 * | 7±3.4 * | 2±1.3 * | 22±3.9 * | 13±4.0 * | 39.4±7.4 * |

Table 8. Data from 75ml 7.5% Icodextrin Rabbits
% Horn Involved

| Right Horn | | | | Left Horn | | | | |
|---|---|---|---|---|---|---|---|---|
| Bowel | Bladder | Itself | Left | Bowel | Bladder | Itself | Right | Overall |
| - | - | - | - | - | - | 10(1) | - | 0.5+ |
| 10(2) | - | 30(1) | - | 10(2) | - | 20(1) | - | 1.0+ |
| - | - | - | - | - | 10(1) | 30(1) | - | 0.5+ |
| 10(1) | 10(1) | 40(1) | - | 10(1) | 10(1) | - | - | 1.5+ |
| 20(2) | - | 30(1) | - | 20(2) | - | - | - | 1.0+ |
| - | - | 10(1) | - | - | - | 50(1) | - | 1.0+ |
| 10(1) | 20(1) | - | 10(1) | 10(1) | 20(1) | 10(1) | 10(1) | 1.5+ |
| - | - | 20(1) | 10(1) | - | - | 30(1) | 10(1) | 1.0+ |
| - | 10(1) | 10(1) | - | - | 10(1) | 10(1) | - | 1.0+ |
| - | - | 20(1) | 20(1) | - | - | 20(1) | 20(1) | 1.0+ |
| 5±2.2 * | 4±2.2 * | 16±4.5 * | 4±2.2 * | 5±2.2 * | 5±2.2 * | 18±4.9 * | 4±2.2 * | 22.5±4.2 * |

Table 9. Data from 10ml 20% Icodextrin Rabbits
% Horn Involved

| Right Horn | | | | Left Horn | | | | |
|---|---|---|---|---|---|---|---|---|
| Bowel | Bladder | Itself | Left | Bowel | Bladder | Itself | Right | Overall |
| 20(2) | - | 50(2) | 30(2) | 20(2) | - | 50(2) | 30(2) | 3.0+ |
| 10(1) | - | 10(1) | 10(1) | 10(1) | - | 50(1) | 10(1) | 2.0+ |
| 40(1) | - | 50(2) | 30(1) | 40(1) | - | 40(1) | 30(1) | 2.5+ |
| 40(1) | 20(1) | 40(1) | 30(2) | 40(1) | 20(1) | 30(1) | 30(2) | 2.5+ |
| - | 20(1) | 10(1) | - | - | 20(1) | 20(1) | - | 1.0+ |
| 30(2) | - | 40(1) | 30(1) | 30(2) | - | 30(1) | 30(1) | 2.5+ |
| 30(1) | 20(2) | 40(1) | 40(1) | 30(1) | 20(2) | 10(1) | 40(1) | 2.5+ |
| 10(1) | - | 50(1) | 20(1) | 10(1) | - | 30(1) | 20(1) | 2.0+ |
| 20(1) | 10(1) | 40(1) | 40(1) | 20(1) | 10(1) | 30(1) | 40(1) | 2.5+ |
| 20(1) | - | 20(1) | 20(1) | 20(1) | - | 40(2) | 20(1) | 2.0+ |
| 22±4.2 | 7±3.0 * | 35±5.0 * | 25±4.0 * | 22±4.2 | 7±3.0 * | 33±4.0 | 25±4.0 * | 78±7.9 * |

Table 10. Data from 15ml 20% Icodextrin Rabbits
% Horn Involved

| Right Horn | | | | Left Horn | | | | |
|---|---|---|---|---|---|---|---|---|
| Bowel | Bladder | Itself | Left | Bowel | Bladder | Itself | Right | Overall |
| - | - | 50(1) | 50(1) | - | - | 50(1) | 50(1) | 2.5+ |
| 20(1) | 20(1) | 20(1) | 20(1) | 20(1) | 20(1) | 20(1) | 20(1) | 2.0+ |
| - | 30(2) | 50(1) | 30(1) | - | 30(2) | 20(1) | 30(1) | 2.5+ |
| 20(1) | 20(1) | 40(1) | 30(1) | 20(1) | 20(1) | 40(1) | 30(1) | 2.0+ |
| 30(1) | 20(1) | 40(1) | 20(1) | 30(1) | 20(1) | 40(1) | 20(1) | 2.0+ |
| 40(2) | 30(2) | 50(1) | 50(1) | 40(2) | 30(2) | 50(1) | 50(1) | 3.0+ |
| 20(1) | - | 20(1) | - | - | - | - | - | 0.5+ |
| - | - | - | 10(1) | - | - | - | 10(1) | 0.5+ |
| - | 20(1) | 10(1) | 10(1) | - | 20(1) | 20(1) | 10(1) | 1.5+ |
| 30(1) | 30(1) | 40(1) | 40(1) | 20(1) | 30(1) | 40(1) | 30(1) | 2.5+ |
| 16±4.8 * | 17±4.0 | 32±5.7 | 25±5.2 * | 14±5.0 * | 17±4.0 | 28±5.9 | 25±5.2 * | 61.3±11.6 * |

Table 11. Data from 25ml 20% Icodextrin Rabbits
% Horn Involved

| Right Horn | | | | Left Horn | | | | |
|---|---|---|---|---|---|---|---|---|
| Bowel | Bladder | Itself | Left | Bowel | Bladder | Itself | Right | Overall |
| 20(1) | - | - | 10(1) | 20(1) | - | 40(2) | 10(1) | 1.5+ |
| 20(1) | 20(1) | 40(1) | - | - | - | 30(1) | - | 1.5+ |
| 10(1) | - | 40(1) | 10(1) | 10(1) | - | 30(1) | 10(1) | 1.5+ |
| 30(1) | - | 40(1) | - | 30(1) | - | 10(1) | - | 1.5+ |
| - | - | 10(1) | 10(1) | - | - | 10(1) | 10(1) | 1.0+ |
| 10(1) | 20(1) | 10(1) | 10(1) | 10(1) | 20(1) | 20(1) | 10(1) | 2.0+ |
| 20(2) | - | 30(1) | 40(2) | 20(2) | - | 30(1) | 40(2) | 2.5+ |
| - | - | 20(1) | 20(1) | - | - | 50(1) | 20(1) | 1.5+ |
| - | - | - | - | - | | 10(1) | - | 0.5+ |
| - | 20(1) | 10(1) | - | - | 20(1) | 20(1) | - | 1.0+ |
| 11±3.5 * | 6±3.1 * | 20±5.2 | 10±3.0 * | 9±3.5 * | 4±2.7 * | 25±4.3 * | 10±3.9 * | 42.5±7.5 * |

Table 12. Data from 50ml 20% Icodextrin Rabbits
% Horn Involved

| Right Horn | | | | Left Horn | | | | |
|---|---|---|---|---|---|---|---|---|
| Bowel | Bladder | Itself | Left | Bowel | Bladder | Itself | Right | Overall |
| - | - | 10(1) | - | - | - | - | - | 0.5+ |
| 10(1) | - | 10(1) | - | - | - | 20(2) | - | 1.0+ |
| 20(1) | - | 20(1) | 10(1) | 20(1) | - | 10(1) | 10(1) | 1.5+ |
| - | 10(1) | - | - | - | - | - | - | 0.5+ |
| - | - | 10(1) | 10(1) | - | - | 20(1) | 10(1) | 1.0+ |
| 30(1) | - | 20(1) | 10(1) | 30(1) | - | 20(1) | 10(1) | 1.5+ |
| - | 10(1) | - | 10(1) | - | 10(1) | 20(1) | 10(1) | 1.5+ |
| - | 20(1) | 40(1) | 30(1) | - | 20(1) | 10(1) | 30(1) | 2.0+ |
| - | 30(1) | 40(1) | 10(1) | - | 30(1) | 20(1) | 10(1) | 2.0+ |
| - | 30(2) | 30(1) | 20(1) | - | 30(2) | 30(2) | 20(1) | 2.0+ |
| 6±3.4 | 10±3.9 * | 18±4.7 * | 10±3.0 | 5±3.4 * | 9±4.1 * | 15±3.1 * | 10±3.0 * | 38.4±7.6 * |

Table 13. Data from 75ml 20% Icodextrin Rabbits
% Horn Involved

| Right Horn | | | | Left Horn | | | | |
|---|---|---|---|---|---|---|---|---|
| Bowel | Bladder | Itself | Left | Bowel | Bladder | Itself | Right | Overall |
| - | - | 10(1) | 10(1) | - | - | 20(2) | 10(1) | 1.0+ |
| - | - | - | - | - | - | 30(1) | - | 0.5+ |
| - | - | 30(1) | 10(1) | - | - | 30(1) | 10(1) | 1.0+ |
| 20(1) | 40(1) | 10(1) | - | 20(1) | 40(1) | 10(1) | - | 2.0+ |
| - | 10(1) | 30(1) | 10(1) | - | 10(1) | 30(1) | 10(1) | 1.5+ |
| 10(1) | 10(1) | 20(1) | 30(1) | 10(1) | 10(1) | 20(1) | 30(1) | 1.5+ |
| - | 30(1) | 10(1) | 10(1) | - | 30(1) | 10(1) | 10(1) | 1.5+ |
| - | - | 40(1) | 10(1) | - | - | 20(1) | 10(1) | 1.5+ |
| - | - | 10(1) | 20(1) | - | - | - | 20(1) | 1.0+ |
| - | - | 10(1) | - | 20(1) | - | - | - | 0.5+ |
| 3±2.1 * | 9±4.5 * | 17±4.0 * | 10±3.0 * | 5±2.7 * | 9±4.6 * | 17±3.7 * | 10±3.0 * | 31.7±6.3 * |

Table 14. Incidence of Adhesion Formation

| | # Sites Free/ # Possible | % Adhesion Free | p Value Control | p Value Placebo |
|---|---|---|---|---|
| Control | 2/80 | 2.5 | | |
| 10ml Placebo | 12/80 | 15.0 | 0.012 | |
| 75ml Placebo | 14/80 | 17.5 | 0.004 | |
| 10ml 7.5% Icodextrin | 12/80 | 15.0 | 0.012 | 1.00 |
| 15ml 7.5% Icodextrin | 6/80 | 7.5 | 0.277 | 0.211 |
| 25ml 7.5% Icodextrin | 31/80 | 38.8 | 0.000 | 0.001 |
| 50ml 7.5% Icodextrin | 32/80 | 40.0 | 0.000 | 0.003 |
| 75ml 7.5% Icodextrin | 44/80 | 55.0 | 0.000 | 0.000 |
| 10ml 20% Icodextrin | 16/80 | 20.0 | 0.001 | 0.533 |
| 15ml 20% Icodextrin | 20/80 | 25.0 | 0.000 | 0.167 |
| 25ml 20% Icodextrin | 34/80 | 42.5 | 0.000 | 0.000 |
| 50ml 20% Icodextrin | 36/80 | 45.0 | 0.000 | 0.000 |
| 75ml 20% Icodextrin | 36/80 | 45.0 | 0.000 | 0.000 |

**DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION**

Attorney Docket No. 9052-67

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled ***DEXTRIN-CONTAINING COMPOSITION FOR PREVENTING SURGICAL ADHESIONS***,

the specification of which

☐ is attached hereto

OR

☒ was filed on **May 13, 1999** as PCT International Application No. **PCT/GB99/01306**.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate, or of any PCT International application having a filing date before that of the application on which priority is claimed.

| | | | |
|---|---|---|---|
| 9810127.2 | GB | 05/13/1998 | ☒ Yes ☐ No |
| Number | Country | MM/DD/YYYY Filed | Priority Claimed |
| | | | ☐ Yes ☐ No |
| Number | Country | MM/DD/YYYY Filed | Priority Claimed |
| | | | ☐ Yes ☐ No |
| Number | Country | MM/DD/YYYY Filed | Priority Claimed |

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

| None | |
|---|---|
| Application Number(s) | Filing Date (MM/DD/YYYY) |
| | |
| Application Number(s) | Filing Date (MM/DD/YYYY) |

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) or § 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application(s) in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application (37 C.F.R. § 1.63(d)).

| PCT/GB99/01306 | 05/13/1999 | Published |
|---|---|---|
| Appln. Serial No. | Filing Date | Status<br>Patented/Pending/Abandoned |
| | | |
| Appln. Serial No. | Filing Date | Status<br>Patented/Pending/Abandoned |
| | | |
| Appln. Serial No. | Filing Date | Status<br>Patented/Pending/Abandoned |

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following registered attorney(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

**Customer Number 20792**

| | |
|---|---|
| Send correspondence to: | Robert J. Smith<br>Myers Bigel Sibley & Sajovec<br>Post Office Box 37428<br>Raleigh, NC 27627 |
| Direct telephone calls to: | Robert J. Smith<br>(919)854-1400 |
| Facsimile: | (919) 854-1401 |

Full name of (first/sole) inventor: Colin Brown

Inventor's Signature: _____ Date: 23 Jan 2001

| | |
|---|---|
| Residence: | United Kingdom |
| Citizenship: | British |
| Post Office Address: | c/o ML Laboratories Plc<br>Blaby Hall<br>Church Street<br>Blaby LE8 4FA England<br>GB |